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Review

Brain membrane lipids in major depression and anxiety disorders ☆

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ABSTRACT

Major depression and anxiety disorders have high prevalence rates and are frequently comorbid. The neurobiological bases for these disorders are not fully understood, and available treatments are not always effective. Current models assume that dysfunctions in neuronal proteins and peptide activities are the primary causes of these disorders. Brain lipids determine the localization and function of proteins in the cell membrane and in doing so regulate synaptic throughput in neurons. Lipids may also leave the membrane as transmitters and relay signals from the membrane to intracellular compartments or to other cells. Here we review how membrane lipids, which play roles in the membrane's function as a barrier and a signaling medium for classical transmitter signaling, contribute to depression and anxiety disorders and how this role may provide targets for lipid-based treatment approaches. Preclinical findings have suggested a crucial role for the membrane-forming n-3 polyunsaturated fatty acids, glycerolipids, glycerophospholipids, and sphingolipids in the induction of depression- and anxiety-related behaviors. These polyunsaturated fatty acids also offer new treatment options such as targeted dietary supplementation or pharmacological interference with lipid-regulating enzymes. While clinical trials support this view, effective lipid-based therapies may need more individualized approaches. Altogether, accumulating evidence suggests a crucial role for membrane lipids in the pathogenesis of depression and anxiety disorders; these lipids could be exploited for improved prevention and treatment.

1. Introduction

With lifetime prevalences of more than 10%, major depressive disorder and anxiety disorders are common mental disorders [12]. These disorders lead to significant suffering for the affected persons and, therefore, belong to the leading diseases in the study of the total global burden of disease [221]. Approximately 10% of patients with depression commit suicide. The causes of these disorders are poorly understood. In this review, we summarize the current status of the relationship between lipids and depression and anxiety disorders.

Lipids play an increasingly recognized role in neuronal function in the brain [21]. The lipid composition of the brain (within single brain regions, specific neuronal subtypes, or even neuronal subcompartments) substantially influences subjective perception, mood and emotional behavior. A large number of lipids can be found in the plasma membrane,

Abbreviations: AC, acid ceramidase; ACTH, adrenocorticotropic hormone; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ASM, acid sphingomyelinase; BDNF, brain-derived nerve growth factor; CB1, cannabinoid 1 receptor; CDP-DAG, cytidine diphosphate diacylglycerol; Cer, ceramide; CerS, ceramide synthases; COPI, coat protein complex I; DA, dopamine; DAG, diacylglycerol; DAT, dopamine transporter; DGK, diacyglycerol kinases; DHA, docosahexaenoic acid (22:6n-3); DOPAC, dihydroxyphenylacetic acid; DPA, docosapentanoic acid (22:5n-6); EPA, eicosapentanoic acid (20:5n-3); EPM, elevated plus maze; ERK, extracellular signal-regulated kinase; FA, fatty acids; FC, frontal cortex; 5-HT, serotonin; 5-HIAA, 5-hydroxyindoleacetic acid; FST, forced swim test; GalCer, galactosylceramide; GlcCer, glucosylceramide; GSL, glycosphingolipids; HVA, homo-vanillic acid; IFNα, interferon α; IL-6, interleukin-6; LPC, lysophosphatidylcholines; MAO, monoamine oxidase; Mfsd2a, major facilitator superfamily domain-containing protein 2; MHPG, 3-methoxy-4-hydroxyphenylglycol; NA, noradrenaline; Nac, nucleus accumbens; NAT, noradrenaline transporter; NMDA, N-methyl-D-aspartate; NSF, novelty suppressed feeding test; NSM, neutral sphingomyelinase; PA, phosphatidic acid; PC, phosphatidylcholines (*synonym*: glycerophosphocholines); PE, phosphatidylethanolamines (*synonym*: glycerophosphoethanolamines); PFC, prefrontal cortex; PI, phosphatidylinositols (*synonym*: glycerophosphoinositols); PIP, phosphoinositides (*synonym*: phosphatidylinositol phosphates); PI3K, PI-3-kinase; PKC, protein kinase C; PLA_2, phospholipase A2; PLC, phospholipase C; PLD, phospholipase D; PS, phosphatidylserines (*synonym*: glycerophosphoserines); PTEN, phosphatase and tensin homolog; PUFAs, polyunsaturated fatty acids; SERT, serotonin transporter; SM, sphingomyelin; SNPs, single nucleotide polymorphisms; S1P, sphingosine-1-phosphate; SPC, sphingosylphosphorylcholine; SphK2, sphingosine kinase 2; SSRI, selective serotonin reuptake inhibitor; TNF-α, tumor necrosis factor alpha; TPH-2, tryptophan hydroxylase-2

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where they regulate the membrane's function as a barrier between the intracellular and extracellular spaces. Membrane lipids can also determine the localization and function of proteins within the membrane and in doing so regulate synaptic throughput. Lipids can influence both exo- and endocytic processes and work within the membrane as second messengers. Lipids may be hydrolyzed and leave the membrane in both directions: as intracellular transmitters, they can relay signals from the membrane to intracellular compartments, and as extracellular transmitters, they can relay information to other cells. This review will focus on membrane lipids, which play roles in the membrane's function as a barrier and a signaling medium for classical transmitter signaling. An overview of the role of membrane-derived extracellular signaling lipids in synaptic function and emotional behavior can be found in other reviews [31,178,223]. The organization of this review follows the lipid classification of LIPID MAPS [56,57].

Membrane lipids have important functions in the brain. Membrane lipids constitute a physical barrier that segregates the inner and outer cellular environments; these lipids are also involved in cell signaling [210]. The lipid fraction of mammalian membranes consists of glycerophospholipids, sphingolipids and the sterol lipid cholesterol. The relative proportions of these components vary a great deal depending on the cell type and the type of membrane [71,210]. Glycerophospholipids use glycerol as a backbone, which carries two long-chain fatty acids (FA) attached at the *sn*-1 and *sn*-2 positions primarily through ester linkages (therefore called *diacylglycerophospholipids*). Polyunsaturated fatty acids (PUFAs) are preferentially attached to the *sn-2* position, while the FA at *sn-1* is usually saturated. The *sn*-3 position is occupied by one of several head groups. The typical glycerophospholipids found in mammalian membranes are phosphatidylcholines (PC; *synonym*: glycerophosphocholines), phosphatidylethanolamines (PE; *synonym*: glycerophosphoethanolamines), phosphatidylserines (PS; *synonym*: glycerophosphoserines) and phosphatidylinositols (PI; *synonym*: glycerophosphoinositols) that are all attached through a phosphodiester linkage. Depending on the cell type, a substantial portion of glycerophospholipids consists of plasmalogens (*1-alkyl,2-acyl glycerophospholipids*) that bear an ether-linked alkyl chain at the *sn*-1 position instead of the ester-linked FA [147]. Plasmalogens are especially abundant in the adult human central nervous system [147] and are thought to play a role in Alzheimer's disease [77]. Sphingolipids, the other abundant lipid category in plasma membranes, are synthesized from ceramide (Cer). Cer is composed of the long-chain amino alcohol sphingosine and a long saturated FA (C16–C32) attached to the 2-amino group via an amide linkage. The major sphingolipids in mammalian membranes are sphingomyelin (SM) and the glycosphingolipids (GSL), which contain mono-, di- or oligosaccharides based on glucosylceramide (GlcCer) or galactosylceramide (GalCer) [114]. Gangliosides are GSL with terminal sialic acids. They are expressed at high abundance and complexity in the brain [186,209]. Cerebrosides are either GlcCer or GalCer and play an important role in myelin function and stability [33].

The lipid classes contribute differentially to the bilayer assembly and the structural demands of biological membranes [210]. The lipid classes also differ in their ability to interact with proteins embedded in the membrane. Recently, a direct and highly specific interaction of exactly one SM species, *N*-stearoyl sphingomyelin (SM 18), with the transmembrane domain of protein p24, a protein involved in coat protein complex I (COPI) vesicle biogenesis, was demonstrated [36], indicating that membrane lipids can act as cofactors to regulate protein function. The acidic phospholipids PS and PI, which are preferentially located in the inner leaflet of the plasma membrane, are specifically recognized by soluble proteins [120]. The association of proteins with the surface of the intracellular membrane is essential for a wide variety of cellular functions. A small portion of the PI pool is further phosphorylated at the 3-, 4- and/or 5-positions to generate one of seven different phosphoinositides (*synonym*: phosphatidylinositol phosphates, PIPs). These lipids can be hydrolyzed into second messengers that mediate acute responses [15] or act as constitutive signals that define organelle identity [47].

The signaling-induced activation of hydrolytic enzymes can lead to the conversion of structural membrane components into regulatory messengers. PC can be converted into phosphatidic acid (PA) through the action of phospholipase D (PLD). PC-specific and PI-specific phospholipase C can remove the head group of phospholipids to yield diacylglycerol (DAG). SM can be converted to Cer by one of several sphingomyelinases. PA, DAG and Cer retain the full hydrophobic portion of their parent molecules and thus remain part of the membrane. They exert their regulatory function either through the recruitment of cytosolic proteins or by changing the biophysical properties of the membrane. In contrast, the removal of a FA from either glycerophospholipids or sphingolipids yields molecules that can readily leave the membrane. Examples include the production of a variety of lysophospholipids (*synonym*: monoacylglycerophospholipids) from their respective glycerophospholipids through the action of phospholipase A_2 (PLA_2), sphingosylphosphorylcholine (SPC) from SM via sphingomyelin deacylase [143] and sphingosine from Cer via ceramidase. Most of their regulatory function can be attributed to their binding to specific receptors. The FA released by these hydrolyses can further act in signal transduction, e.g., PUFA can be converted into eicosanoids.

2. Fatty acids

2.1. Preclinical evidence

The lipid composition of the brain can be altered with long-term changes in diet. This effect may have direct consequences on mood and emotional behavior. A highly palatable diet particularly rich in fat and low in proteins (often called the “cafeteria diet”) fed to rats for 8 weeks after weaning induced overweight status, higher adiposity, and a higher liver weight, as well as a reduction in anxiety-like behaviors in the open field and elevated plus maze (EPM) anxiety tests. This diet has also been shown to reduce general locomotor activity but increase social interactions and aggression, reduce pain threshold [22,116,168], and potentiate the anxiolytic effects of repeated foot shock stress [160]. These findings suggest that enhancing the general availability of lipids in the brain may have an anxiolytic/antidepressant effect. Nonetheless, the anxiolytic potential of this diet may be age-dependent and gender-specific with stronger effects in females [116,218]. The maternal intake of a high-energy diet enriched in PUFAs induced higher locomotor activity in the open field, increased levels of aggressive behavior in the resident intruder test, and had antidepressant-like effects in the forced swim test (FST) in mouse offspring [177].

The dietary effects on locomotor activity may thus depend on when PUFAs are enriched during development. Increased locomotion may occur if the supply is high during the prenatal time and weaning. The opposite effect can be observed if PUFAs are chronically increased only after weaning. Interestingly, a diet that was highly palatable due to an increased carbohydrate content also increased body weight and fat mass in rats but increased anxiety-like behavior in the light–dark test [197]. The anxiolytic/antidepressant effect of a diet is hypothesized to result not primarily from its palatability and increased expression of eating behavior but rather an increased lipid supply [168]; however, see also [137]. A study on susceptibility to chronic unpredictable stress, which may trigger depression-related behavior [164,222], suggested that the combination of a high-fat plus high-carbohydrate diet most effectively protects rats against a stress-induced increase in corticosterone levels [226].

Brain membranes contain a high proportion of PUFAs, with n-3 FA being the most prevalent in the brain's gray matter [20,193]. n-3 PUFAs cannot be synthetized de novo by mammals but must be obtained from the diet. The incorporation of these FA into the brain

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